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PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark
Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 30 October 1997 (30.10.97)	
International application No. PCT/IL97/00117	Applicant's or agent's file reference Y/96-23 PCT
International filing date (day/month/year) 01 April 1997 (01.04.97)	Priority date (day/month/year) 02 April 1996 (02.04.96)
Applicant WALLACH, David et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
09 October 1997 (09.10.97)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer I. Britel
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification 6 : C12N 15/12, 15/54, C07K 14/47, C12N 9/12, 1/19, 15/81, 1/21, 5/10, 15/85, 15/86, C07K 16/18, 16/40, C12N 15/11, 9/00, A61K 48/00</p>	<p>A1</p>	<p>(11) International Publication Number: WO 97/37016 (43) International Publication Date: 9 October 1997 (09.10.97)</p>
<p>(21) International Application Number: PCT/IL97/00117 (22) International Filing Date: 1 April 1997 (01.04.97) (30) Priority Data: 117800 2 April 1996 (02.04.96) IL 119133 26 August 1996 (26.08.96) IL (71) Applicant (for all designated States except US): YEDA RESEARCH AND DEVELOPMENT CO. LTD. [IL/IL]; Weizmann Institute of Science, P.O. Box 95, 76100 Rehovot (IL). (72) Inventors; and (75) Inventors/Applicants (for US only): WALLACH, David [IL/IL]; 24 Borochoy Street, 76406 Rehovot (IL). MALININ, Nikolai [RU/IL]; Weizmann Institute of Science, Beit Clore, 76100 Rehovot (IL). BOLDIN, Mark [RU/IL]; Weizmann Institute of Science, Beit Clore, 76100 Rehovot (IL). KOVALENKO, Andrei [RU/IL]; Weizmann Institute of Science, Beit Clore, 76100 Rehovot (IL). METT, Igor [IL/IL]; 60 Levin Epstein Street, 76462 Rehovot (IL). (74) Agent: EINAV, Henry; Inter-Lab Ltd., Science-based Industrial Park, Kiryat Weizmann, 76110 Ness-Ziona (IL).</p>	<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>	
<p>(54) Title: MODULATORS OF TNF RECEPTOR ASSOCIATED FACTOR (TRAF), THEIR PREPARATION AND USE</p>		
<p>(57) Abstract</p> <p>A DNA sequence encoding a protein capable of binding to a tumor necrosis factor receptor-associated factor (TRAF) molecule, TRAF-binding proteins, their isoforms, analogs, fragments and derivatives encoded by the DNA sequence, their methods for the production of the DNA sequences and proteins, and the uses for the DNA sequence and proteins.</p>		

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

EINAV, Henry
INTER-LAB Ltd.
Science-based Industrial Park
Kiryat Weizmann
Ness-Ziona 76100
ISRAEL

**NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

(PCT Rule 71.1)

Date of mailing
(day/month/year)

13.07.98

Applicant's or agent's file reference
Y/96-23 PCT

IMPORTANT NOTIFICATION

International application No
PCT/IL97/00117

International filing date (day/month/year)
01/04/1997

Priority date (day/month/year)
02/04/1996

Applicant
YEDA RESEARCH AND DEVELOPMENT CO. LTD. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.


4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference Y/96-23 PCT	FOR FURTHER ACTION		See Notification of Transmittal of International Preliminary Examination Report (PCT/IPEA/416)
International application No. PCT/IL97/00117	International filing date (day/month/year) 01/04/1997	Priority date (day/month/year) 02/04/1996	
International Patent Classification (IPC) or national classification and IPC C12N15/12			
Applicant YEDA RESEARCH AND DEVELOPMENT CO. LTD. et al.			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 38.



2. This REPORT consists of a total of 11 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 09/10/1997	Date of completion of this report 13.07.98
Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx 523656 apmu d Fax: (+49-89) 2399-4465	Authorized officer Kalsner, I Telephone No. (+49-89) 2399-8708 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**International application No. **PCT/IL97/00117****I. Basis of the report**

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1- 64 as originally filed

Claims, No.:

1- 49 as originally filed

Drawings, sheets:

1/46- 46/46 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non- establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non- obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
☒ claims Nos. 19, 20.

because:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/IL97/00117

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 19, 20 are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
- ☐ paid additional fees.
- ☐ paid additional fees under protest.
- ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

- ☐ complied with.
- ☒ not complied with for the following reasons:

see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- ☒ all parts.
- ☐ the parts relating to claims Nos. .

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**International application No. **PCT/IL97/00117****V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement****1. Statement**

Novelty (N)	Yes:	Claims	5, 7- 12, 18, 22- 29, 31- 49
	No:	Claims	1- 4, 6, 13- 17, 21, 30
Inventive step (IS)	Yes:	Claims	5, 7- 12, 18, 31, 35- 39, 41, 42, 46- 48
	No:	Claims	1- 4, 6, 13- 17, 21- 30, 32- 34, 40, 43- 45, 49
Industrial applicability (IA)	Yes:	Claims	1- 18, 21- 49
	No:	Claims	

2. Citations and explanations**see separate sheet****VI. Certain documents cited****1. Certain published documents (Rule 70.10)**

and / or

2. Non- written disclosures (Rule 70.9)**see separate sheet****VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:

see separate sheet**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/IL97/00117

Ad section III

The protein referred to in claim 19 ("NIK") is defined by reference to several DNA sequences according to claims 1- 12. It appears, though, that "NIK" is supposed to be the name of a single distinct protein. Reference to several different DNA sequences (e.g. in claim 4) renders the claim fully unclear so that examination of claim 19 and dependent claim 20 cannot be carried out.

Ad Section IV

This authority wholly agrees with the objection put forward by the International Searching Authority (ISA) in its letter of 18/08/97 as to lack of unity (Rules 13.1- 13.3 PCT).

An international application must relate to one invention only or to a group of inventions so linked as to form a single general inventive concept.

Unity of invention is fulfilled only when there is a technical relationship among the inventions involving one or more of the same special technical features, special technical features being such features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

This special technical feature of the present application appears to be a protein which binds to a tumour necrosis factor receptor- associated factor (TRAF).

As the existence of such proteins is already known in the state of the art (see Section V, par. 2) the application no longer meets the requirements concerning unity of invention.

The present application, thus, falls apart in the following groups of inventions:

Invention 1: Claims 1- 6, 13- 17, 21- 30, 32- 37, 40, 43- 45, 49, all partially:

A DNA sequence encoding a protein capable of binding to tumour necrosis factor receptor- associated factor (TRAF) molecule as depicted in Fig. 3/SEQ ID NO:1/clone 9, fragments, variants and hybridising molecules thereof; vectors and

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/IL97/00117

transformed cells; TRAF- binding protein encoded by said DNA, isoforms, fragments, analogs and derivative thereof; method for their production; antibodies; uses of DNA, protein, antibodies, oligonucleotides, ribozyme for modulation of cell signalling activity mediated by TRAF2; method for isolating and identifying proteins capable of binding to TRAF2 and of modulating the cellular activity of TRAF2; pharmaceutical compositions comprising said protein, DNA, oligonucleotide, and therapeutical uses thereof; methods for screening a ligand capable of binding to said protein.

Invention 2: Claims 7- 12, 18- 20, 31, 38, 39, 41, 42, 46- 48 (all totally), claims 1- 4, 12- 18, 21- 30, 32- 37, 40, 43, 44, 45, 49 (all partially):

A DNA sequence encoding a protein capable of binding to tumour necrosis facto receptor- associated factor (TRAF) molecule as depicted in Fig. 4 and 6/SEQ ID NO:3 and 6/clone 10, fragments, variants and hybridising molecules thereof; vectors and transformed cells; TRAF- binding protein encoded by said DNA, isoforms, fragments, analogs and derivative thereof; method for their production; antibodies; uses of DNA, protein, antibodies, oligonucleotides, ribozyme for modulation of cell signalling activity mediated by TRAF2; method for isolating and identifying proteins capable of binding to TRAF2 and of modulating the cellular activity of TRAF2; pharmaceutical compositions comprising said protein, DNA, oligonucleotide, and therapeutical uses thereof; methods for screening a ligand capable of binding to said protein.

Invention 3: Claims 1- 6, 13- 17, 21- 30, 32- 37, 40, 43- 45, 49 (all partially):

A DNA sequence encoding a protein capable of binding to tumour necrosis facto receptor- associated factor (TRAF) molecule as depicted in Fig. 5/SEQ ID NO:4/clone 15, fragments, variants and hybridising molecules thereof; vectors and transformed cells; TRAF- binding protein encoded by said DNA, isoforms, fragments, analogs and derivative thereof; method for their production; antibodies; uses of DNA, protein, antibodies, oligonucleotides, ribozyme for modulation of cell signalling activity mediated by TRAF2; method for isolating and identifying proteins capable of binding to TRAF2 and of modulating the cellular activity of TRAF2; pharmaceutical compositions comprising said protein, DNA, oligonucleotide, and therapeutical uses thereof; methods for screening a ligand capable of binding to said protein.

According to Rule 68.1 PCT, the IPEA chose, however, not to invite the applicant to restrict the claims or to pay additional fees, as examination could be carried out

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/IL97/00117

without effort justifying to invite payment of additional fees .

Ad section V**1) Documents:**

D1...Rothe et al. (1995) Cell 83:1243- 1252

D2...Mosialos et al (1995) Cell 80: 389- 399

2) Novelty

D1 describes two proteins (inhibitor of apoptosis protein; IAP1, IAP2), which associate with tumour necrosis factor receptor- associated factors 1 and 2 (TRAF1, TRAF2). The binding of these proteins to TRAF occurs within TRAF's cytoplasmic domain (amino acids 264- 501; p. 1247, lines 4- 6).

D2 describes a human protein (LMP1) which has been shown to interact with a protein termed LMP1 associated protein 1 (LAP 1) and which is homologous to TRAF2 (see summary). LMP1 was shown to induce NF- κ B activation (p. 80, left col., lines 16- 19).

In view of D1 and D2 **claims 1- 4, 6, 13- 17, 21 and 30** are not considered novel in the sense of Art. 33(2) PCT.

2.1 Claims 1- 3 and 6 cannot be considered novel as they refer to a DNA sequence encoding a protein capable of binding to a TRAF molecule, the TRAF molecule being TRAF2 and the binding site being located within amino acids 222- 501 of TRAF2. As the claimed subject- matter is defined merely by the result to be achieved, lacking any technical (=structural) features, both D1 and D2 are novelty destroying for these claims.

2.2 Claim 4 does not meet the requirements of Art. 33(2) PCT as it refers to a "DNA sequence capable of hybridising ... under moderately stringent conditions ...". Depending on the hybridisation conditions, almost any given DNA sequence can hybridise to the claimed DNA sequences (see also section VIII, par. 2). Thus, the

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International application No. PCT/IL97/00117

DNA encoding the TRAF2 binding protein disclosed in D1 (c- IAP) is considered novelty destroying for claim 4.

- 2.3 **Claims 13- 16** are directed to a vector comprising a DNA sequence according to claims 1- 12, capable of being expressed in either eukaryotic or prokaryotic cells as well as the respective transformed host cell. As the experiments described in D1 and D2 are based on recombinant technology, and thus disclose vectors and transformed cells, claims 13- 16 are not considered novel in view of these documents.
- 2.4 **Claims 17 and 21** do not meet the requirements of Art. 33(2) PCT as TRAF binding proteins which bind to the portion of the TRAF2 protein between the amino acids 222- 501 of TRAF2, as well as a method for producing the protein, are disclosed in D1 (p. 1247, lines 5, 6 and p. 1250, left col., last three par's.).
- 2.5 **Claim 30** lacks novelty as a method for isolating and identifying proteins capable of binding directly to TRAF2 applying the yeast two- hybrid procedure is disclosed in D1.
- 2.6 **Claims 5, 7- 12, 18, 22- 29 and 31- 49** are considered to meet the requirements of Art. 33(2) PCT, because the subject- matter of these claims is not disclosed as such in any of the available prior art.

3) Inventive step

- 3.1 **Claim 22** relating to an antibody specific for a TRAF binding protein does not meet the requirements of Art. 33(3) PCT, as providing an antibody directed to a known protein cannot be considered to involve an inventive step.
- 3.2 As it is known from D1 that activity of NF- κ B is modulated by TRAF2 and factors associated with it, methods for modulating the activity of NF- κ B by TRAF2, methods for modulating TRAF2 mediated effects on cells, as well as methods for treatment of a pathological condition associated with NF- κ B induction making use of TRAF2 binding proteins (which are known) are not considered to involve an inventive step. **Claims 23- 29 and 40** thus, do not meet the requirements of Art

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EXAMINATION REPORT - SEPARATE SHEET

33(3) PCT.

- 3.3 **Claims 32- 34** relating to pharmaceutical compositions for modulating the TRAF2 mediated effect on cells do not meet the requirements of Art. 33(3) PCT. As TRAF2 binding proteins and their effects are known in the art (D1, D2), providing a pharmaceutical composition comprising these known proteins cannot be considered to involve an inventive step.
- 3.4 **Claims 43 and 44** do not meet the requirements of Art. 33(3) PCT as methods for screening of a ligand capable of binding to a protein according to claims 17- 20 (i.e., e.g. TRAF2) employing techniques known in the art (affinity chromatography or yeast two- hybrid procedure) cannot be considered to involve an inventive step.
- 3.5 Since ligands capable of modulating the cellular activity mediated by TRAF2 are known in the art, **claims 45 and 49** which refer to methods of identifying and producing ligands with similar properties or structures cannot be considered to involve an inventive step.
- 3.6 **Claims 5, 7- 12 and 18**, directed to specific DNA sequences and provided they are clearly and unambiguously defined are considered to meet the requirements of Art. 33(3) PCT.
- 3.7 Any of the claims directed to methods and pharmaceutical compositions specifically referring to a DNA sequence which is considered novel (i.e. **claims 31, 35- 39, 41, 42 and 46- 48**) are considered to meet the requirements of Art. 33(3) PCT.
- 4) As it is understood from the description (p. 17, lines 10, 11), claims 23- 29 include methods for treatment. Regarding the positive statement as to industrial applicability of **claims 23- 29 and 40** the following should be noted: For the assessment of said claims on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject- matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/IL97/00117

compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

- 5) The priority claimed for the present application has been checked and is considered valid.

Ad section VI

The applicant's attention is drawn to the following document which is cited in the Search Report as "E" document, and therefore can be considered relevant for the assessment of novelty of the present application, once entered in the European regional phase:

WO 9706182, published 20 February 1997, filed 6 August 1996 with priority dates of 8 August 1995 and 8 December 1995.

Ad section VII

The following inconsistencies in the description have been noted:

- 1) p. 17: references to the figures is incorrect
- 2) p. 52: reference to tables is incorrect (table 2 is referred to as table 1).
- 3) Fig. 7: on pages containing fig. 7 b, d, f, h, j, l, n, p, r, t, v, x, z, and ab parts of the sequences are missing.

Ad section VIII

The following claims do not meet the requirements of Art. 6 PCT:

- 1) **Claims 4, 11, 12, 46, 47** refer to DNA sequences which are merely defined by reference to a figure. According to the Guidelines (III, 4.10) "the claims must not, in respect of the technical features of the invention, rely on references to the description or drawings...". These claims, thus lack clarity in the sense of Art. 6

INTERNATIONAL PRELIMINARY

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EXAMINATION REPORT - SEPARATE SHEET

PCT.

- 2) Furthermore **claims 4 and 10** are considered unclear because they refer to a DNA sequence which is "capable of hybridising ... under moderately stringent conditions ...". As the actual hybridisation conditions are not defined these claims do not meet the requirements of Art. 6 PCT.
- 3) In a number of claims (i.e. **claims 4, 5 7, 18, 35, 38, 41**) the DNA sequence is defined by reference to a clone (clones 9, 10 and 15). As these clones are not defined in any way the claims are not considered clear in the sense of Art. 6 PCT.
- 4) **Claims 8- 12, 19, 20, 22, 31, 36, 37, 39, 42, and 46- 48** refer to a protein ("NIK") merely by arbitrary designation without defining it by technical (=structural) features. Said claims are therefore not clear, contrary to the requirements of Art. 6 PCT.

PATENT COOPERATION TREATY

PCT

22/155676

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference Y/96-23 PCT	FOR FURTHER ACTION <small>see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.</small>	
International application No. PCT/IL 97/00117	International filing date (day/month/year) 01/04/1997	(Earliest) Priority Date (day/month/year) 02/04/1996
Applicant YEDA RESEARCH AND DEVELOPMENT CO. LTD. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 7 sheets.
☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☒ Certain claims were found unsearchable (see Box I).
2. ☒ Unity of invention is lacking (see Box II).
3. ☒ The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing

☐ filed with the international application.
☒ furnished by the applicant separately from the international application,
 ☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.

☐ Transcribed by this Authority
4. With regard to the title, ☒ the text is approved as submitted by the applicant
 ☐ the text has been established by this Authority to read as follows:
5. With regard to the abstract, ☒ the text is approved as submitted by the applicant
 ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.
6. The figure of the drawings to be published with the abstract is:

☐ as suggested by the applicant. ☒ None of the figures.
☐ because the applicant failed to suggest a figure.
☐ because this figure better characterizes the invention.

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 23-29 as far as in vivo methods are concerned and 40-42 is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See Form PCT/ISA/210 (continuation sheet)

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

1) claims 1-6, 13-17, 21-30, 32-37, 40, 43-45, 49 all partially.

A DNA sequence encoding a protein capable of binding to tumor necrosis factor receptor-associated factor (TRAF) molecule as depicted in Fig. 3a / Seq.ID:1 / clone 9, fragments, variants and hybridizing molecules thereof. Vectors and transformed host cells. Traf-binding protein encoded by said DNA, isoforms, fragments, analogs and derivative thereof and method for their production. Antibodies. Uses of DNA, protein, antibodies, oligonucleotides, ribozyme for modulation of cell signaling activity mediated by TRAF2. Method for isolating and identifying proteins capable of binding to TRAF2 and of modulating the cellular activity of TRAF2. Pharmaceutical composition comprising said protein, DNA, oligonucleotide, and therapeutical uses thereof. Methods for screening a ligand capable of binding to said protein.

2) claims 7-12, 18-20, 31, 38, 39, 41, 42, 46-48 all totally; claims 1-4, 6, 12-18, 21-30, 32-37, 40, 43, 44, 45, 49 all partially.

A DNA sequence encoding a protein capable of binding to tumor necrosis factor receptor-associated factor (TRAF) molecule as depicted in Fig. 4,6 / Seq.ID:3,6 / clone 10, fragments, variants and hybridizing molecules thereof. Vectors and transformed host cells. Traf-binding protein encoded by said DNA, isoforms, fragments, analogs and derivative thereof and method for their production. Antibodies. Uses of DNA, protein, antibodies, oligonucleotides, ribozyme for modulation of cell signaling activity mediated by TRAF2. Method for isolating and identifying proteins capable of binding to TRAF2 and of modulating the cellular activity of TRAF2. Pharmaceutical composition comprising said protein, DNA, oligonucleotide, and therapeutical uses thereof. Methods for screening a ligand capable of binding to said protein.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

3) claims 1-6, 13-17, 21-30, 32-37, 40, 43-45, 49 all partially.

A DNA sequence encoding a protein capable of binding to tumor necrosis factor receptor-associated factor (TRAF) molecule as depicted in Fig. 5a / Seq.ID:4 / clone 15, fragments, variants and hybridizing molecules thereof. Vectors and transformed host cells. Traf-binding protein encoded by said DNA, isoforms, fragments, analogs and derivative thereof and method for their production. Antibodies. Uses of DNA, protein, antibodies, oligonucleotides, ribozyme for modulation of cell signaling activity mediated by TRAF2. Method for isolating and identifying proteins capable of binding to TRAF2 and of modulating the cellular activity of TRAF2. Pharmaceutical composition comprising said protein, DNA, oligonucleotide, and therapeutical uses thereof. Methods for screening a ligand capable of binding to said protein.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IL 97/00117

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/12 C12N15/54 C07K14/47 C12N9/12 C12N1/19
 C12N15/81 C12N1/21 C12N5/10 C12N15/85 C12N15/86
 C07K16/18 C07K16/40 C12N15/11 C12N9/00 A61K48/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C07K A61K C12Q G01N C07H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CELL, vol. 83, no. 7, 29 December 1995, pages 1243-1252, XP002032302 ROTHE M ET AL: "THE TNFR2-TRAF SIGNALING COMPLEX CONTAINS TWO NOVEL PROTEINS RELATED TO BACULOVIRAL INHIBITOR OF APOPTOSIS PROTEINS" cited in the application see abstract	1-3, 13-17, 21-30, 43-45, 49
A	see page 1246, right-hand column, line 29 - page 1248, left-hand column, line 26 see page 1249, right-hand column, line 60 - page 1250, left-hand column, line 38 see page 1250, right-hand column, line 31-44 --- -/--	6, 32-34, 40

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

4 August 1997

Date of mailing of the international search report

18. 08. 97

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INTERNATIONAL SEARCH REPORT

Intern. Application No

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K38/17 A61K38/45 C12Q1/68 C12Q1/48 C12Q1/66
 G01N33/68 C07K19/00 C12N15/62 //(C12N1/19,
 C12R1:865)

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	<p>WO 97 06182 A (TULARIK INC) 20 February 1997</p> <p>see page 3, line 1 - page 13, line 17 see page 30 - page 31; claims --- -/-</p>	<p>1-3, 13-17, 21, 23-25, 27,28, 30, 32-34, 40,44, 45,49</p>

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Date of the actual completion of the international search

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>NATURE, vol. 385, 6 February 1997, pages 540-544, XP002036441 MALININ N L ET AL: "MAP3K-RELATED KINASE INVOLVED IN NF-kB INDUCTION BY TNF, CD95 AND IL-1" see the whole document ---</p>	<p>1-4, 6-14, 16-21, 23,24, 30,31, 44-49</p>
P,X	<p>GENES AND DEVELOPMENT, vol. 10, no. 8, 15 April 1996, pages 963-973, XP000607798 CHENG G ET AL: "TANK, A CO-INDUCER WITH TRAF2 OF TNF-AND CD40L-MEDIATED NF-KB ACTIVATION" cited in the application see abstract see page 966, right-hand column, paragraph 2 - page 971, left-hand column ---</p>	<p>1,6</p>
A	<p>CELL, vol. 80, 10 February 1995, pages 389-399, XP002036476 MOSIALOS G ET AL: "THE EPSTEIN-BARR VIRUS TRANSFORMING PROTEIN LMP1 ENGAGES SIGNALING PROTEINS FOR THE TUMOR NECROSIS FACTOR RECEPTOR FAMILY" cited in the application see abstract see page 394, left-hand column, line 45 - page 395, left-hand column, line 4; figure 6B ---</p>	<p>1,6</p>
A	<p>TRENDS IN CELL BIOLOGY, vol. 5, October 1995, pages 392-399, XP002036717 VANDENABEELE P ET AL: "TWO TUMOUR NECROSIS FACTOR RECEPTORS: STRUCTURE AND FUNCTION" cited in the application -----</p>	

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No

PCT/IL 97/00117

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9706182 A	20-02-97	AU 6692996 A	05-03-97
